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A Facile Synthesis of New Heterocyclic Compounds from Thiourea and Urea, which Links with Some Hexoses

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Abstract

Background: Thiourea was considered as an important compound which produced industrial chemical products, and synthesis of heterocyclic compounds. Urea and thiourea derivatives were an important in purification factors for organic and inorganic wastes. The research methodology deals with three component cycloaddition phenols and urea with benzaldehyde in the presence of absolute ethanol at 80°C for 8 h, under reflux after compellation reaction the product linkage with some sugar.

A series of new thiourea and urea derivatives have synthesized by the reaction of multicomponent such as phenol, benzaldehyde and urea or thiourea to yield a new amides derivatives 4a, 4b and 6a, 6b respectively. The amide compounds have condensed with a different monosaccharide sugars like (D-glucose, D-galactose, and D-fructose) afforded new N-glucoside compounds.

Keywords: Thiourea; Urea; N-glucosides ; D-Glucose

Introduction

There are a large number of antibiotics and chemotherapeutics for medical uses although antibacterial agents created a new antimicrobial resistance in the last decade's [1-4]. Thiourea is consider an important compounds which produce industrial chemical products, and at synthesis of heterocyclic compounds [5]. Urea and thiourea derivatives are an important in purification factors for organic and inorganic wastes [6]. Thiourea and urea derivatives exhibited a high biological activity

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[7,8] act as antiviral, anticancer, anticonvulsant, analgesic and HDL-elevating properties [9]. Thiourea is one of the most important organic compounds: shows marked biological activity, such as corrosion inhibitors, antioxidant, and polymer compounds [10]. Furthermore, the nucleosides in addition to modified C-nucleoside, which have a large number of medical properties such as antiviral, antibiotic and antitumor activities [11-15]. We reported that newly synthesized compounds attachment with carbohydrate moieties to increase the biological activities of urea and thiourea derivatives.

Results and Discussion

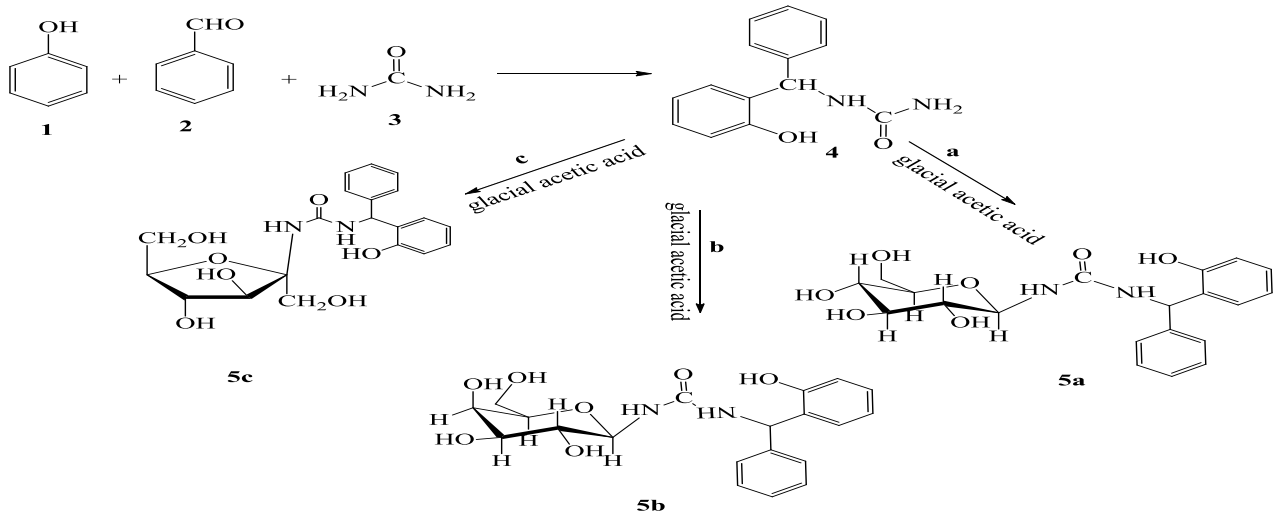
The goal of the research is to prepare urea and thiourea derivatives and then interact it with some of the monosaccharides such as D-glucose, D-galactose and D-fructose to give glycosides derivatives.

Compound 4 was prepared by condensation of phenol and urea with benzaldehyde in the presence of absolute ethanol at 80 °C for 8 h in yield 78%. The compound 4 has characterized by 1HNMR and IR spectra. yielded 78% followed by condensation with equimolar amounts from a series of monosaccharide sugars such as D-glucose, D-galactose and D-fructose in presence of acetic acid used as catalyst yielded cyclic glycosides derivatives 5a, b and c, respectively. The structure of all compounds have confirmed by 1HNMR and IR spectra. The configuration of all glycosides derivatives were β based on indication from 1HNMR where the coupling constant (J=6 to 7MHz) of anomeric protons in these compounds.

Scheme 1

The IR spectrum showed all compounds gave absorption bands from 3250 to 3425 cm^{-1} due to the O–H and N–H stretching vibration and appears another strong band at 1642 to 1686 cm^{-1} due to carbonyl vibration of the amide. 1HNMR of compound 4 showed a peak at 9.03 ppm due to (CO–NH) group and also appeared another signal around at 7.63 ppm

SCHEME 1. **Synthesis of N-glucoside Compounds 5a, 5b and 5c.**



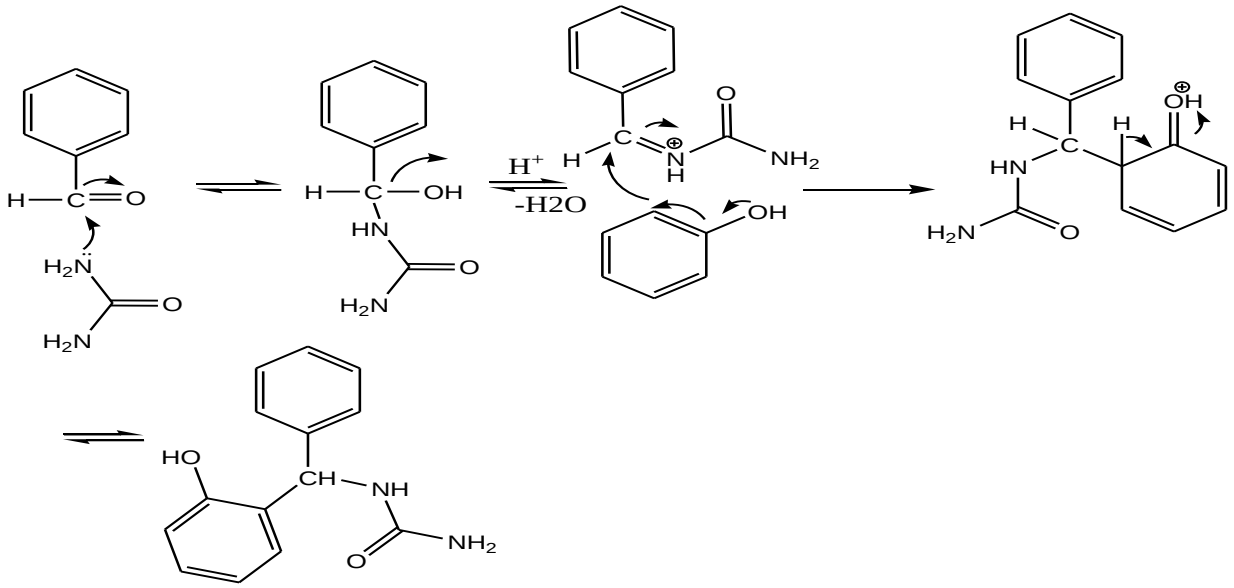
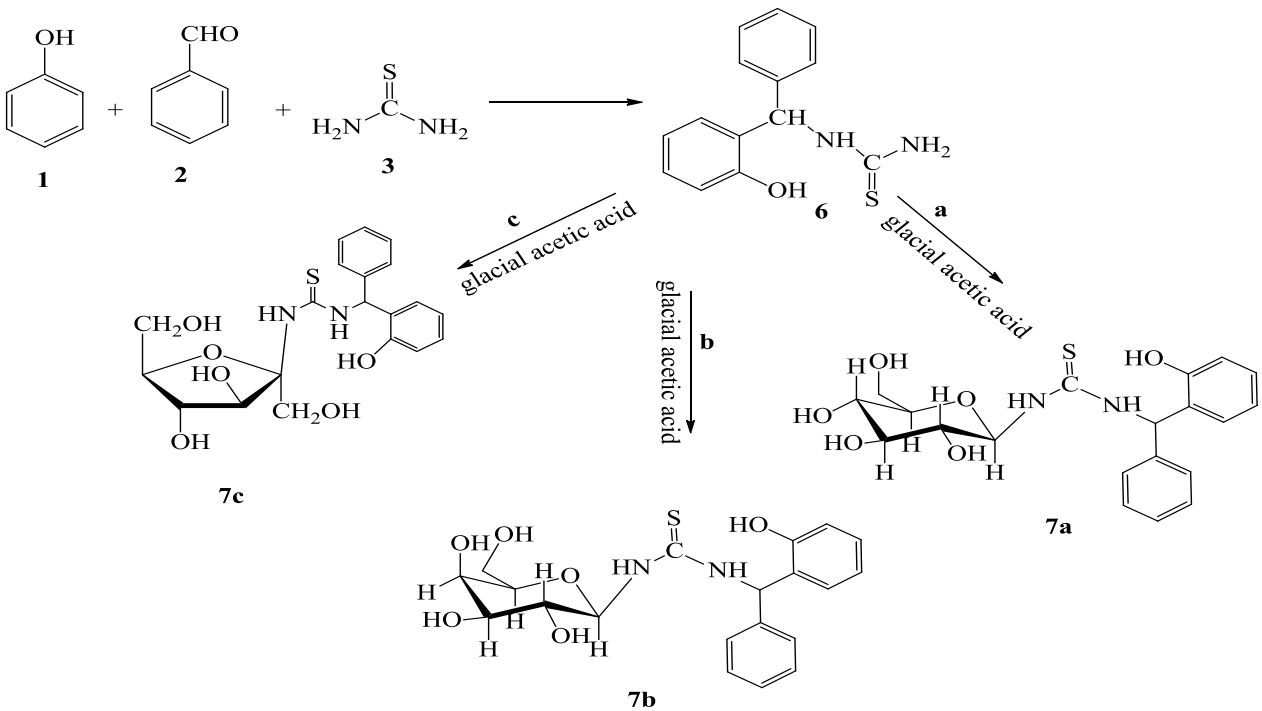


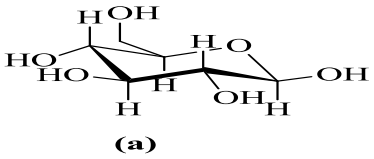
FIG. 1**. Predicted mechanism of synthesis compound 4.**

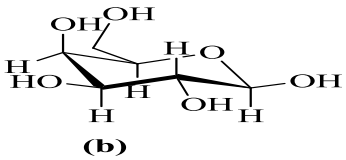
Scheme 2

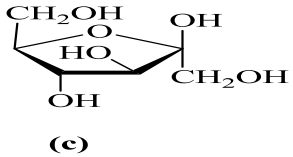
The suggested mechanism for cyclization of compound 4 according to The Biginelli reaction in Scheme 2. Similarly, the multi components of phenol and thiourea with benzaldehyde 2 in absolute ethanol afforded compounds 6 followed by coupling with different monosaccharides sugar gave compounds 7a, 7b and 7c.

SCHEME 2. **Synthesis of *N*-glucoside Compounds 7a, 7b and 7c.**




(a)


(b)


(c)

Experimental Section

General procedures

Melting points were determined on Electro thermal IA 9,100 series digital melting point apparatus in capillaries and are uncorrected. IR spectra were obtained in the solid state as potassium bromide discs using a Perkin-Elmer model 1430 spectrometer. 1HNMR spectra were recorded on a Varian/Gemini 400 MHz spectrometer in DMSO-d6 as a solvent and TMS as an internal standard (chemical shifts in δ, ppm). Mass spectra were measured on an instrument VG-7035 at 70 or 15 eV. Elemental analyses have performed at the Micro analytical Centre, Cairo University, Giza, Egypt.

General Procedure for the synthesis of 4 and 6: A mixture of benzaldehyde (1 mmol), anhydrous phenol (1 mmol), thiourea and/or urea (1 mmol) was allowed to heat at 100°C for different hours with stirring. The process of reactions is monitored by TLC. The reaction mixture has evaporated under vacuum. The residue recrystallization by methanol.

1-((2-hydroxyphenyl) (phenyl) methyl) urea (4): Yield 89%; m.p. 123-125°C; IR (KBr) ν=3383, 3275, 3174, 1613, 1412, 1468 cm-1; 1HNMR (400 MHz, DMSO): δ 9.03 (s, 1H, NH), 7.63 (s, 2H, NH2), 6.83-7.82 (m, 9H, Ar-H), 6.02 (s, 1H, OH), 5.27 (s, 1H, C-H). Anal. Calcd for: C14H14N2O2, (242.27): C, 69.41; H, 5.82; N, 11.56. Found: C, 69.43; H, 5.80; N, 11.59.

1-((2-hydroxyphenyl) (phenyl) methyl) thiourea (6): Yield 86%; m.p. 152-154 °C; IR (KBr) ν=3423, 3256, 3061, 1529, 1213, cm-1; 1HNMR (400 MHz, DMSO): δ 10.21 (s, 1H, NH), 8.24 (s, 2H, NH2), 6.83-7.82 (m, 9H, Ar-H), 5.27 (s, 1H, OH), 4.95 (s, 1H, C-H). Anal. Calcd for: C14H14N2OS, (258.34): C, 65.09; H, 5.46; N, 10.84; S, 12.41. Found: C, 65.18; H, 5.42; N, 10.64; S, 12.39.

General Procedure for the Synthesis of 5a, 5b, 5c and 7a, 7b, 7c: A mixture of amide derivatives 4 or 6 (1 mmol) and series monosaccharide (1mml) was refluxed in absolute ethanol (10 ml) in the presence of drops of glacial acetic acid for 6 h. After cooling the solid was filtered off and recrystallized from ethanol.

1-((2-hydroxyphenyl) (phenyl) methyl)-3-(1-deoxy-β-D-glucopyranosyl) urea (5a): Yield 76%; m.p. 144-146 °C; IR: 3416-3378 (OH), 1679 (C=O), 1610 (C=N). 1HNMR (400 MHz, DMSO): δ 3.40-3.43 (m, 2H, H-6`,6``), 3.46 (m, 1H, H-5`), 3.32 (m, 1H, H-4`), 3.27 (t, J=7.4 Hz, 1H, H-3`), 4.71 (dd, J=7.4 Hz, J=7.8 Hz, 1H, H-2`), 4.42 (m, 1H, OH), 4.79 (d, J=6.4 Hz, 1H, OH), 6.52 (d, 1H, J=6.6 Hz, H`1), 6.18 (s, 2H NH), 5.63 (t, J=4.6 Hz, 1H, OH), 7.02-7.32 (m, 9H, Ar-H), 5.27 (s, 1H, OH), 4.60 (s, 1H, C-H). Anal. Calcd. for: C20H24N2O7,(404.42): C, 59.40; H, 5.98; N, 6.93. Found: C, 59.38; H, 5.96; N, 6.96.

1-((2-hydroxyphenyl) (phenyl) methyl)-3-(1-deoxy-β-D-galactopyranosyl) urea (5b): Yield 59%; m.p. 110-112°C; IR: 3510-3480 (OH), 1678 (C=O), 1612 (C=N). 1HNMR (400 MHz, DMSO): δ 3.72-3.59 (m, 2H, H-6`,6``), 3.62 (m, 1H, H-5`), 3.32 (m, 1H, H-4`), 3.27 (t, J=7.4 Hz, 1H, H-3`), 3.27 (dd, J=7.4 Hz, J=7.8 Hz, 1H, H-2`), 4.46 (m, 1H, OH), 4.49 (d, J=6.4

Hz, 1H, OH), 6.34 (d, 1H, J=6 Hz, H`1)5.63 (t, J=4.6 Hz, 1H, OH), 5.79 (t, J=4.6 Hz, 1H, OH), 6.11 (s, 2H, NH). IR: Anal. Calcd for: Anal. Calcd. for: C20H24N2O7,(404.42): C, 59.40; H, 5.98; N, 6.93. Found: C, 59.37; H, 5.98; N, 6.95.

1-((2-hydroxyphenyl) (phenyl) methyl)-3-(1-deoxy-β-D-fructopyranosyl) urea (5c): Yield 68%; m.p. 177-179 °C; IR: 3410-3380 (OH), 1674 (C=O), 1615 (C=N). 1HNMR (400 MHz, DMSO): δ 8.03 (s, 1H, NH), 6.93-7.32 (m, 9H, Ar-H), 6.32 (s, 1H, C-H), 5.63 (s, 1H, OH), 3.63-3.57 (m, 5H, 2`-H, 3`-H, 4`-H, 5`-H, 6`,6``-H), 3.02 (s,2H,CH2). Anal. Calcd for: C20H24N2O7, (404.41): C, 59.40; H, 5.98; N, 6.93. Found: C, 59.44; H, 5.97; N, 6.94.

1-((2-hydroxyphenyl) (phenyl) methyl)-3-(1-deoxy-β-D-glucopyranosyl)thiourea (7a): Yield 56%; m.p. 155-157 °C; IR: 3410-3380 (OH), 1674 (C=O), 1615 (C=N). 1HNMR (400 MHz, DMSO): δ 3.76-3.59 (m, 6H, H-6`,6``, H-5`, H-4`, H-3`, H-2`), 4.53 (m, 1H, OH), 4.49 (d, J=6.4 Hz, 1H, OH), 7.30 (m, 1H, H`), 5.33 (s, 1H, OH), 5.65 (t, J=4.6 Hz, 1H, OH), 5.79 (t, J=4.6 Hz, 1H, OH), 9.36 (s, 1H, NH). δ Anal. Calcd for: C20H24N 2O6S, (420.48): C, 57.13; H, 5.75; N, 6.66; S, 7.63. Found: C, 57.17; H, 5.72; N, 6.63; S, 7.67

1-((2-hydroxyphenyl)(phenyl)methyl)-3-(1-deoxy-β-D-galactopyranosyl)thiourea (7b): Yield: 69.5%; m.p. 148-150°C; IR: 3400-3375 (OH), 1674 (C=O), 1615 (C=N). 1HNMR (400 MHz, DMSO): δ1HNMR (400 MHz, DMSO): δ 3.62-3.49 (m, 3H, H-6`,6``, H-5`), 3.32-3.27 (m, 3H, H-4`, H-3`, H-2`), 4.46 (m, 1H, OH), 4.49 (d, J=6.4 Hz, 1H, OH), 7.19 (m, 1H, H1`), 5.65 (t, J=4.6 Hz, 1H, OH), 5.69 (t, J=4.6 Hz, 1H, OH), 7.23 (s, 2H, NH). Anal. Calcd for: C20H24N2O6S, (420.48): C, 57.13; H, 5.75; N, 6.66; S, 7.63. Found: C, 57.11; H, 5.71; N, 6.62; S, 7.64

1-((2-hydroxyphenyl) (phenyl) methyl)-3-(1-deoxy-β-D-fructopyranosyl) thiourea (7c): Yield 73%; m.p. 199-201°C; IR: 3450-3204 (OH), 1668 (C=O), 1595 (C=N). 1HNMR (400 MHz, DMSO): δ 6.12 (s, 1H, NH), 6.96-7.42 (m, 9H, Ar-H), 5.82 (s, 1H, C-H), 5.43 (s, 1H, OH), 3.63-4.05 (m, 5H, 2`-H, 3`-H, 4`-H, 5`-H, 6`,6``-H), 3.21(s,2H,CH2). Anal. Calcd for: C20H24N2O6S, 420.48: C, 57.13; H, 5.75; N, 6.66; S, 7.63. Found: 57.15; H, 5.73; N, 6.63; S, 7.63.

Conclusions

In summary, we have synthesized novel new compounds by three compounds condensation of urea or thiourea with benzaldehyde and phenol to produce 1-((2-hydroxyphenyl) (phenyl) methyl) urea 4 and 1-((2-hydroxyphenyl) (phenyl) methyl) thiourea 6. These compounds have linkage with monosaccharides such as glucose, galactose and fructose to afford N-glycosides compounds.

Conflict of Interest

The authors confirm that this article content has no conflict of interest.

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